

AMENDMENTS TO THE SPECIFICATION:

Please amend the specification as follows:

Please replace the paragraphs on page 6, lines 3-7, with the following amended paragraphs:

Figure 7A shows the amino acid sequence of a murine GDF-8 propeptide-Fc fusion protein, as provided in SEQ ID NO:20.

Figure 7B shows a murine GDF-8 propeptide-Fc fusion protein with a short glycine-serine-glycine-serine (GSGS, SEQ ID NO:17) linker separating the GDF-8 propeptide from the Fc region, as provided in SEQ ID NO:21.

Please replace the paragraphs on page 6, lines 18-21, with the following amended paragraphs:

Figure 11A shows the amino acid sequence of a human GDF-8 propeptide IgG1 Fc fusion protein, as provided in SEQ ID NO:22.

Figure 11B shows the amino acid sequence of a human GDF-8 propeptide-IgG1 Fc fusion protein modified for reduced effector function, as provided in SEQ ID NO:23.

Please replace the paragraph on page 18, lines 3-15, with the following amended paragraph:

Critically, in embodiments of the invention involving modified GDF propeptides comprising fusion proteins, it is essential that the fusion protein be produced or designed such that the native proteolytic cleavage site (e.g. RSRR (SEQ ID NO:18)) in the GDF propeptide is disrupted, destroyed, inactivated or removed in the resulting fusion protein. As one of skill in the art will recognize, failure to do so would result in the second protein (e.g., the stabilizer portion) of the fusion protein being cleaved from the

first protein (the propeptide portion) of the fusion protein. Accordingly, a critical aspect of the invention provides for inactivating or eliminating the cleavage site native to GDF propeptides when using such propeptide to prepare a fusion protein which is a modified GDF propeptide of the invention. Methods for inactivating such proteolytic cleavage sites are known in the art and include but are not limited to mutation, deletion, or insertion of the amino acid or nucleotide sequence of the proteolytic cleavage site.

Please replace the paragraph on page 21, lines 14-21, with the following amended paragraph:

In an alternate embodiment, the cDNA constructs used for expression of such fusion proteins may contain nucleotides encoding a linker peptide between the nucleotides encoding the GDF propeptide and the IgG Fc region (or stabilizer portion). The orientation of the linker peptide relative to the GDF or IgG Fc region is unimportant. The linker peptide may comprise nucleotides encoding 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30 or more amino acids in length. In a particular embodiment, the linker peptide comprises nucleotides encoding for the amino acid sequence consisting of glycine-serine-glycine-serine (GSGS, SEQ ID NO:17).

Please replace the paragraph bridging pages 23 and 24, beginning on page 23, line 17 and continuing until page 24, line 4, with the following amended paragraph:

The proteolytic or synthetic GDF-8 and BMP-11 propeptide portions of the modified GDF propeptide may comprise as many amino acid residues as are necessary to bind to the target GDF protein, thereby inhibiting, partially or completely, GDF-8 or BMP-11 activity. Examples 4 - 6, herein, illustrate embodiments of binding and inhibition assays. In particular, functional fragments of GDF-8 and/or BMP-11

propeptide sequences that maintain the ability to modulate or inhibit GDF-8, are included within the scope of the invention. The GDF-8 propeptide portions preferably comprise at least 5, 10, 20, 30, 40, 50, 60, 70, 80, or 90 amino acids; more preferably at least 100, 110, 120, 130, 140, 150, 160, 170, 180, or 190 amino acids; and most preferably at least 200, 210, 220, 230, or 240 or more amino acids in length. In a preferred embodiment, the GDF-8 propeptide portion of the modified GDF-8 propeptide is 243 amino acids in length, i.e., corresponding to SEQ ID NO:5; and the BMP-11 propeptide portion of the BMP-11 propeptide is 274 amino acids in length, i.e., corresponding to SEQ ID NO:11. The signal sequence for human GDF-8 is set forth in SEQ ID NO:13, and includes the first 23 amino acids of SEQ ID NO:1. In one embodiment, the sequence of BMP-11 propeptide begins with the amino acid sequence AEGPAAA (SEQ ID NO:19).

Please also amend the specification by replacing the prior sequence listing with the sequence listing filed herewith.